UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JAN 25 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Ad hoc Peer Review of Glyphosate (Round Up)
Caswell # 661A

TO: Addressees

Attached for your review and consideration are:

1. A draft DER by Dynamac on a mouse oncogenic study (Biodynamics BDN-77-420)

2. TOX Branch memo of September 9, 1984 concerning this study.

3. Monsanto submission (March 20, 1984) concerning historical control data.

4. A preliminary risk quantification based on the mouse study; and

5. A brief synopsis of other pivotal studies on Glyphosate.

The Committee is expected to review the evidence and provide a concensus opinion on Glyphosate.

The meeting will be held Monday, February 11, 1985 - 9:30 - 11:30 am in Dr. Farber's office. Further questions may be addressed to Dr. W. Dykstra. Please follow the present policy not to prepare official reviews of the material presented. You may, however, wish to bring notes or handouts to the meeting in support of your line of discussion. When a concensus is reached, an official memorandum will be prepared.

Reto Engler, Ph.D.
Chief, Scientific Mission Support Staff
Toxicology Branch

Addressees: T. Farber
W. Burnam
G. Paynter
H. Lacayo
B. Litt
W. Dykstra
C. Chaisson
S. Saunders
L. Chitlik

cc: Section Heads
C. Gordon
J. Quest
B. Coberly

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Glyphosate; Summary of Pivotal Toxicology Studies

TO: Reto Engler, Ph.D.
Chief, SMSS
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D. William Dykstra 11/24/85
Toxicology Branch
Hazard Evaluation Division (TS-769)

- Mutagenicity: negative in the following studies.
  - a. Rec-assay in two strains of B. subtilis up to 2000 ug/test.
  - b. Reverse Mutation in 5 histidine - requiring strains of S. typhimurium and 1 tryptophan-requiring strain E. coli, with and without metabolic activation.
  - c. Ames test in four strains of Salmonella, with and without metabolic activation.
  - d. Dominant lethal study in the mouse at 2000 mg/kg.
  - e. DNA repair in rat hepatocytes between 1.25×10^{-5} and 1.25×10^{-1} mg/ml.
  - f. In vivo bone marrow cytogenetic up to 1000 mg/kg.
  - g. Chinese Hamster Ovary gene mutation with and without metabolic activation.
- Teratology
  - a. Rat; negative for terata up to 3500 mg/kg (HDT) during days 6-15 of gestation. Maternal LEL was 3500 mg/kg and effects were death, inactivity, decreased body weight. The LEL in fetuses was 3500 mg/kg and effect was delayed ossification in sternabrae. Fetotoxic and maternal NOEL was 1000 mg/kg.

b. Rabbit; negative for terata up to 350 mg/kg/day (HDT) during days 6-27 of gestation. Maternal LEL: 350 mg/kg/day; Effects at LEL were death, diarrhea, nasal discharge.
Maternal NOEL: 175 mg/kg/day.
Fetotoxic NOEL: 350 mg/kg/day (HDT).

o Three-generation reproduction study in rats:

NOEL is 10 mg/kg/day (mid-dose). LEL is 30 mg/kg/day (high-dose); effect at high-dose was histological findings of renal tubular dilation in F_{3b} male weanlings.

o Twenty-six month chronic/oncogenic feeding study in rats:

Systemic NOEL: 30 mg/kg/day (HDT). Based on re-evaluation of thyroid slides in female rats by Dr. Capen, it was concluded that the oncogenic potential was negative at 30 mg/kg/day (HDT).

o Evaluation of ADI:

Based on the NOEL of 10 mg/kg/day in the rat reproduction study and using a safty factor of 100, the ADI = $\frac{10 \text{ mg/kg/day}}{100}$ = 0.1 mg/kg/day.

DRAFT

MEMORANDUM

TO: Toxicology Branch Ad-hoc Peer Review Group
(TS-767C)

FROM: Herbert Lacayo, Statistician Herbert Lacayo Jr Jan 22, 1985
Mission Support Staff
Toxicology Branch/HED (TS-767C)

SUBJECT: Prelimary Risk Assessment for Glyphosate

Summary

This memo contains an estimate of potency for Glyphosate based on kidney tubule adenomas in male mice (ref 1). That data yields a Q_1*, of 5.9×10^{-5} for mg/kg/day. Determination of the weight of the biological evidence (ref 2) or worker and dietary risks are not considered here.

Background

The DER currently being performed by Dynamac has identified no statistically significant tumor findings. However, the kidney tubule adenomas reported (ref 1) are considered to be

rare tumors by Dr. L. Kasza (Toxicology Branch pathologist). For this reason we have taken the worst case approach. No dietary or worker data have been considered. This information has now been requested.

The experimental design (ref 4) consists of groups of 50 male and 50 female randomized CD-1 mice, individually caged, which were administered diets containg 0, 1000, 5000, 30,000 ppm of test material for 24 months. The animal data summarized below were provided by William Dykstra's review of Glyphosate (ref 4).

Glyphosate, Kidney Tubule Adenomas In CD-1 Male Mice

Dose (ppm)	0	1000	5000	3000
TBA/Total	0/49	0/49	1/50	3/50

TBA = Tumor bearing Animal

Total = Total number of animals in the group

Remarks on Statistical Significance

We ~~wish to~~ make some ~~important~~ observations concerning statistically significant dose response before proceeding to estimate Q_1^*.

First, the data are statistically significant (using the Cochran-Armitage dose response test) at the $p \leq .05$ level. This could be a function of the spacing of the doses. Second, none of the pairwise comparisons (using Fisher's exact test) were significant at the $p \leq .05$ level.

Note that the above tests do not incorporate any historical data which might yield an accurate estimate of the ~~false~~ event rate for controls. Now suppose there are no events in a control group of 100 mice (something that could easily happen with a low tumor rate) and that there are 3 events out of 50 in the high dose group. Such a scenario would establish (using Fisher's exact test) statistical significance at the $p = .03$ level.

As a more direct example (of how historical data might effect statistical significance) assume that the historical tumor rate (for kidney tubule adenomas) is 1/100 (or 1/1000), then the occurrence of 3 events in 50 mice becomes significant

at p=.015 (or p=.0001). This example should make clear the importance of using ~~any~~ reliable historical rates for rare tumors.

Low Dose Extrapolation

The mouse dosage was converted from ppm to human equivalent dose in mg/kg/day, based on a 38 gram mouse (ref 4) and a 3 gram diet (ref 5). This equivalence is given below; details of the conversion are given in the appendix.

Mice Dose (ppm)	0	1000	5000	30,000
Human Eq. Dose (mg/kg/day)	0	6.78	33.9	203.39

Following the standard procedures in the EPA Draft Guidelines (ref 2), the human eqivalent dosages and the tumor response data given above were fit with the multihit model. The results are given below.

Chi Square, Q_1*, and Maximum Likelihood Estimate (MLE) of Q_1 for Male Mice In the Glyphosate Feeding Study:

Chi Sq (df)	Q_1* for (mg/kg/day)	MLE of Q_1
1.91 2	5.9×10^{-5}	2.4×10^{-5}

Note that the fit is reasonable in the sense that the multihit model isn't rejected by the Chi Sq statistic (i.e., Chi Sq of 1.91 with 2 df gives a p value between .5 and .75); and that the estimates for Q_1* and Q_1 are close. This implies that the data are of reasonable quality and also that the multihit model is appropriate.

References

1. A Chronic feeding study of Glyphosate in mice (Biodynamics # BDN-77-420; Project No. 77-2061; July 21, 1983).

2. EPA Draft, Revised Interim Guidelines for the Health Assessment of Suspected Carcinogens, August 20, 1984.

3. Memo from Bertram Litt to Statistics Team. Subject: Procedures for Expressing Extimates of Public Health Risks, November 30, 1984.

4. Memo from William Dykstra to Robert Taylor. Subject: Glyphosate; EPA Registration No. 524-308; mouse oncogenicity study. Caswell # 661A, Accession No. 251007-014

5. Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, Published by the Association of Food and Drug Officials of the United States, 1959 (Third Printing 1975)

Appendix

Conversion of ppm dose in mice to mg/kg/day for humans

Assumptions:

i. Mouse eats 3 gms of food per day = 3000 mg/day (see ref 5).

ii. Mouse weighs 38 grms = 0.38 kgs (see ref 1).

iii. Human weighs 60 kg (ref 5).

Calc of mg/kg/day for 38 gm mouse eating 3 gms per day when the mouse dosage is given in ppm

mg/kg/day = (ppm x 3000 mg of food)/.038/day

$$= \frac{(\text{Parts} \times 3000)}{10^6}/.038/\text{day}$$

$$= 7.8947 \times 10^{-2} \times \text{Parts with units in (mg/kg/day)}.$$

DRAFT

Mice ppm Dose	0	1000	5000	30000
Mice dose in (mg/kg/day)	0	78.947	394.7368	2368.4210

Calc of human equivalent dose (mg/kg/day) when mouse dose is in (mg/kg/day).

d_h = dose in mg/kg/day for a human

d_a = dose in mg/kg/day for an animal

W_h = weight of a human

W_a = weight of an animal

$$d_h = d_a \times (W_a/W_h)^{1/3}$$

Or,

$$d_h = .085877116\ d_a$$

This Last equation will give the results in the memo.

Monsanto

Monsanto Company
1101 17th Street, N. W.
Washington, D. C. 20036
Phone: (202) 452-8860

March 20, 1984

MAR 22 1984

Received

Delivered to R. J. Taylor

Date 23 Mar 84

By

Director
Registration Division (TS767C)
Office of Pesticide Programs
U. S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall #2, Room 716D
Arlington, Virginia 22202

Attention: Mr. Robert J. Taylor
Product Manager (25)

Subject: Roundup® Herbicide
EPA Reg. No. 524-308
Additional Information Relating
to Chronic Mouse Study,
BD-77-420

Dear Sir:

On July 29, 1983, Monsanto submitted to the Agency an eight volume report entitled "A Chronic Feeding Study of Glyphosate in Mice," BD-77-420. The accession numbers 251007-251014 were assigned to this submission.

Several weeks ago the Agency requested verbally that we provide historical data for the incidence of renal tubular adenomas in control groups in comparable studies conducted by Bio/dynamics, Inc.

Enclosed with this letter are the requested historical control data. In addition, we have enclosed historical control data from Hazleton Laboratories and International Research and Development Corp. In summary, the data show the following:

a) In the seven studies at Bio/dynamics, listed as studies A-G on the attached table, renal tubular adenomas were observed in the control group in two studies, A (1/54 or 1.9%), and E (2/60 or 3.3%). These studies were conducted during 1978-1981 timeframe.

b) The control group incidence in comparable studies conducted by International Research and Development was 0-1.4%.

c) The incidence in control group mice at Hazleton has been as high as 7.1% (1/14.)

As stated in Dr. Dirks's summary of the chronic mouse study with glyphosate, we consider the slightly increased incidence of adenomas in this study to be spurious and unrelated to treatment. This position is based on the following points:

a) The lesion was observed only in males.

b) The incidence in either the high- or mid-dose groups was not statistically different from control and there was not a statistically significant dose-treatment relationship.

c) Historical control data from Bio/dynamics and other laboratories indicate that these lesions do occur occasionally in comparable ranges.

We hope this information resolves any concern you may have had relative to this issue. If you should have any additional questions, please feel free to contact me or our Washington office.

Sincerely,

Robert W. Street

Robert W. Street
Manager, Product Health
and Safety Information

RWS/jr

cc: Mr. L. L. Gingerich

Male Charles River CD-1 Mice
Bio/dynamics, Inc.

K I D N E Y

C O N T R O L D A T A

STUDY I.D.	A		B		C		D		E		F		G	
	*	**	*	**	*	**	*	**	*	**	*	**	*	**
Tissue/Finding														
Neoplasm														
# Examined	57	54	61	60	51	53	59	60	60	60	60	60	60	60
B - tubular adenoma		01								02				

* Control Group A	Start	6/78	12/77	12/77	10/78	11/78	11/77	10/77
** Control Group B	Terminate	7/80	4/80	3/80	4/81	4/81	4/80	4/80

FEB 9 1984

International Research
and Development Corporation

February 6, 1984

Dr. Richard C. Dirks
Senior Product Toxicologist
Monsanto Company
800 North Lindbergh Blvd.
St. Louis, Missouri 63167

Dear Dr. Dirks:

Listed below is a summary of historical control data on kidney tumors in male Charles River CD-1 mice in studies conducted at IRDC.

Data Base*	Total Male Animals Examined	Tumor Diagnosis	Total # of Animals with Tumors	Total % Incidence	Range of % Incidence in Studies
6 Studies (18-months, 1971-1975)	340	No kidney tumors reported			
7 Studies (20-22 months, 1973-1978)	473	Adenoma	1	0.2	0-2.0
19 Studies (24-25 months, 1976-1978)	1490	Adenoma	3	0.2	0-1.3
		Carcinoma	4	0.3	0-1.7
14 Studies (2-year, 1977-1981)	1360	Adenoma, cortical	2	0.15	0-1.0
		Adenoma, cortical cell	1	0.07	0-1.7
		Tubular adenoma	2	0.15	0-1.4
		Adenoma	2	0.15	0-1.0
		Adenocarcinoma	1	0.07	0-1.0

*Number of studies, average duration of studies, years during which studies were conducted.

Sincerely,

Dale E. Johnson, Pharm.D., Ph.D.
Associate Director, Toxicology Division

DEJ:bf

Mattawan, Michigan 49071 U.S.A. • telephone: (616) 668-3336 • telex: 224302 • cable: IRDC MAAN

HAZLETON
LABORATORIES AMERICA, INC.
9200 LEESBURG TURNPIKE, VIENNA, VIRGINIA 22180 U.S.A.

REPRESENTATIVE HISTORICAL CONTROL DATA

PART I:	RODENT LONGEVITY
PART II:	NEOPLASIA IN SPRAGUE-DAWLEY RATS
PART III:	NEOPLASIA IN UNTREATED B6C3F1 MICE
PART IV:	NEOPLASIA IN B6C3F1 CONTROL MICE TREATED WITH CORN OIL IN THE DIET
PART V:	NEOPLASIA IN B6C3F1 CONTROL MICE TREATED WITH CORN OIL ADMINISTERED BY GAVAGE
PART VI:	NEOPLASIA IN B6C3F1 CONTROL MICE TREATED WITH CARBOXYMETHYL-CELLULOSE ADMINISTERED BY GAVAGE
PART VII:	NEOPLASIA IN UNTREATED CD-1® MICE
PART VIII:	NEOPLASIA IN UNTREATED CD-1® F1 MICE
PART IX:	NEOPLASIA IN CD-1® CONTROL MICE TREATED WITH DISTILLED WATER ADMINISTERED BY GAVAGE
PART X:	NEOPLASIA IN CD-1® CONTROL MICE TREATED WITH 0.5% TRAGACANTH IN DISTILLED WATER ADMINISTERED BY GAVAGE
PART XI:	HEMATOLOGY REFERENCE RANGES
PART XII:	CLINICAL CHEMISTRY REFERENCE RANGES

Hazleton Laboratories America, Inc.: Representative historical control data. Part VII: Neoplasia in untreated CD-1® mice, pg 5. Part VIII: Neoplasia in untreated CD-1® F1 mice, pg 5. July 6, 1983.

NOTE: Historical control data generated in-house at Hazleton Laboratories America, Inc.

HAZLETON LABORATORIES AMERICA, INC.
SUMMARY OF NEOPLASIA IN UNTREATED CONTROL CD-1® F1 MICE

THE FINDINGS PRESENTED IN THIS SUMMARY ARE FROM UNTREATED F1 GENERATION CONTROL MICE SACRIFICED AFTER 91 TO 105 WEEKS.

THE TERM 'POSITIVE TOTALS' REPRESENTS THE TOTAL NUMBER OF POSITIVE FINDINGS FROM STUDIES WHERE THERE WERE ONE OR MORE OCCURRENCES OF THE INDICATED NEOPLASM IN EACH SEX. THE DATA FROM THESE STUDIES, INCLUDING THE NUMBER OF TISSUES EXAMINED, ARE PRESENTED.

THE TERM 'OVERALL TOTALS' REPEATS THE TOTAL NUMBER OF POSITIVE FINDINGS AND ALSO PRESENTS THE TOTAL NUMBER OF TISSUES OBSERVED FROM ALL QUALIFYING STUDIES, THAT IS, THOSE STUDIES WITH POSITIVE AS WELL AS NEGATIVE FINDINGS.

WHEN POSITIVE FINDINGS ARE LISTED FOR TISSUE MASS, OTHER LESIONS, MULTIPLE ORGANS, OR OTHER NON-PROTOCOL TISSUES, THE TOTAL NUMBER OF TISSUES EXAMINED REPRESENTS THE TOTAL NUMBER OF ANIMALS EXAMINED AT THAT INTERVAL OR THE TOTAL NUMBER OF ANIMALS ON STUDY, AS APPROPRIATE.

WHERE INDIVIDUAL STUDY DATA ARE FOLLOWED BY THE SUPER-SCRIPT 'A', THE NUMBER PRESENTED REPRESENTS THE NUMBER OF ANIMALS SACRIFICED AT TERMINATION RATHER THAN THE NUMBER OF TISSUES EXAMINED.

'OVERALL PERCENT' IS THEN CALCULATED USING THE 'OVERALL TOTALS' FIGURE.

THE COMPUTER ESTABLISHES 'RANGE OF PERCENTAGES' FROM THE DATA COMPRISING 'POSITIVE TOTALS'.

NEOPLASIA IN CD-1® F1 MICE-UNTREATED CONTROLS

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)	POSITIVE FINDINGS (FEMALES)	ANIMALS EXAMINED (FEMALES)
*** TISSUE NAME--KIDNEY ***				
TUBULAR CELL ADENOMA				
	1	15	0	15
	1	14	0	26
POSITIVE TOTALS--	2	29	0	41
OVERALL TOTALS---	2	56	0	81
OVERALL PERCENT--	3.6		0.0	
RANGE OF PERCENTAGES--	7 --	7	0 --	0
TUBULAR CELL CARCINOMA				
	1	15	0	15
POSITIVE TOTALS--	1	15	0	15
OVERALL TOTALS---	1	56	0	81
OVERALL PERCENT--	1.8		0.0	
RANGE OF PERCENTAGES--	7 --	7	0 --	0
*** TISSUE NAME--LIVER ***				
HEMANGIOSARCOMA				
	0	15	2	15
POSITIVE TOTALS--	0	15	2	15
OVERALL TOTALS---	0	75	2	100
OVERALL PERCENT--	0.0		2.0	
RANGE OF PERCENTAGES--	0 --	0	13 --	13

Glyphosate

Gordon

JELLINEK, SCHWARTZ, CONNOLLY & FRESHMAN, INC.
1350 NEW YORK AVENUE, N.W., SUITE 400
WASHINGTON, D.C. 20005
(202) 783-3388

STEVEN D. JELLINEK

7 Feb 8

Ted:

The attached is for your information.

I've also sent a copy to John Delaney.

Presumably, you will receive the original through channels.

Regards,

Steve